Fifth Edition

CASARETT & DOULL'S TOXICOLOGY

THE BASIC SCIENCE OF POISONS

毒理学

Curtis D. Klaassen

世界图书出版公司

CASARETT AND DOULL'S TOXICOLOGY

THE BASIC SCIENCE OF POISONS

Fifth Edition

McGraw-Hill
HEALTH PROFESSIONS DIVISION

New York St. Louis San Francisco Auckland Bogotá Caracas Lisbon London Madrid
Mexico City Milan Montreal New Delhi San Juan Singapore Sydney Tokyo Toronto

(陕)新登字 014

陕版出图字　著作权合同登记　25-1998-106 号

ISBN　007-1164391

This edition is permitted by arrangement with McGraw-Hill Book Co. Singapore

Casarett & Doull's Toxicology
Casarett & Doull's 毒理学
by Curtis D. Klaasen et. al.
任卫军　重印责任编辑
世界图书出版西安公司　重印发行
（西安市 南大街 17 号　邮编 710001）
西安七二二六印刷厂印刷
787 × 1092 毫米　开本 1/16　印张 70.5
1999 年 6 月第 1 次重印
ISBN 7-5062-4016-5/R·350
定价：420.00 元

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PREFACE

The fifth edition of *Casarett and Doull's Toxicology: The Basic Science of Poisons* marks its twentieth anniversary. The fifth edition, as the previous four, is meant to serve primarily as a text for, or an adjunct to, graduate courses in toxicology. Because the four previous editions have been widely used in courses in environmental health and related areas, an attempt has been made to maintain those characteristics that make it useful to scientists from other disciplines. This edition will again provide information on the many facets of toxicology and especially on the principles, concepts, and modes of thought that are the foundation of the discipline. Mechanisms of toxicity are emphasized. Research toxicologists will find this book an excellent reference source to find updated material in areas of their special or peripheral interests.

While the overall framework of the fifth edition is similar to the previous four, it has undergone some significant changes. Previously there were five sections, but the present edition has seven sections plus an appendix. The seven sections are "General Principles of Toxicology" (Unit 1), "Disposition of Toxicants" (Unit 2), "Nonorgan-Directed Toxicity" (carcinogenicity, mutagenicity, and teratogenicity) (Unit 3), "Target Organ Toxicity" (Unit 4), "Toxic Agents" (Unit 5), "Environmental Toxicology" (Unit 6), and "Applications of Toxicology" (Unit 7).

Without permitting the fifth edition to become unwieldy in size and prohibitive in cost, we have added three new chapters: "Toxicokinetics," "Mechanisms of Toxicity," and "Toxic Responses of the Endocrine System," as well as an Appendix on "Recommended Limits for Exposure to Chemicals." Half of the thirty-four chapters of the fifth edition have been written by authors not associated with the fourth edition.

The fifth edition reflects the marked progress made in toxicology this decade. For example, the importance of apoptosis, cytokines, growth factors, oncogenes, cell cycling, receptors, gene regulation, transcription factors, transgenic animals, polymorphisms, etc., in understanding the mechanisms of toxicity are included in this edition. More information on risk assessment is also included. The book has many more figures than previously to make it more "user-friendly."

The editor is grateful to our colleagues in academia, industry, and government who have made useful suggestions for improving this fifth edition both as a book and as a reference source. The editor is especially grateful to all the contributors, whose combined expertise has made possible a volume of this breadth. I dedicate this edition to John Doull and Mary Amdur, who have edited previous editions of this book and remain as Editors Emeriti to advise and help me on this fifth edition.

PREFACE TO THE FIRST EDITION

This volume has been designed primarily as a textbook for, or adjunct to, courses in toxicology. However, it should also be of interest to those not directly involved in toxicologic education. For example, the research scientist in toxicology will find sections containing current reports on the status of circumscribed areas of special interest. Those concerned with community health, agriculture, food technology, pharmacy, veterinary medicine, and related disciplines will discover the contents to be most useful as a source of concepts and modes of thought that are applicable to other types of investigative and applied sciences. For those further removed from the field of toxicology or for those who have not entered a specific field of endeavor, this book attempts to present a selectively representative view of the many facets of the subject.

Toxicology: The Basic Science of Poisons has been organized to facilitate its use by these different types of users. The first section (Unit I) describes the elements of method and approach that identify toxicology. It includes those principles most frequently invoked in a full understanding of toxicologic events, such as dose-response, and is primarily mechanistically oriented. Mechanisms are also stressed in the subsequent sections of the book, particularly when these are well identified and extend across classic forms of chemicals and systems. However, the major focus in the second section (Unit II) is on the systemic site of action of toxins. The intent therein is to provide answers to two questions: What kinds of injury are produced in specific organs or systems by toxic agents? What are the agents that produce these effects?

A more conventional approach to toxicology has been utilized in the third section (Unit III), in which the toxic agents are grouped by chemical or use characteristics. In the final section (Unit IV) an attempt has been made to illustrate the ramifications of toxicology into all areas of the health sciences and even beyond. This unit is intended to provide perspective for the nontoxicologist in the application of the results of toxicologic studies and a better understanding of the activities of those engaged in the various aspects of the discipline of toxicology.

It will be obvious to the reader that the contents of this book represent a compromise between the basic, fundamental, mechanistic approach to toxicology and the desire to give a view of the broad horizons presented by the subject. While it is certain that the editors' selectivity might have been more severe, it is equally certain that it could have been less so, and we hope that the balance struck will prove to be appropriate for both toxicologic training and the scientific interest of our colleagues.

L.J.C.
J.D.

Although the philosophy and design of this book evolved over a long period of friendship and mutual respect between the editors, the effort needed to convert ideas into reality was undertaken primarily by Louis J. Casarett. Thus, his death at a time when completion of the manuscript was in sight was particularly tragic. With the help and encouragement of his wife, Margaret G. Casarett, and the other contributors, we have finished Lou's task. This volume is a fitting embodiment of Louis J. Casarett's dedication to toxicology and to toxicologic education.

J.D.

NOTICE

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required. The editors and the publisher of this work have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication. However, in view of the possibility of human error or changes in medical sciences, neither the editors nor the publisher nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they are not responsible for any errors or omissions or for the results obtained from use of such information. Readers are encouraged to confirm the information contained herein with other sources. For example and in particular, readers are advised to check the product information sheet included in the package of each drug they plan to administer to be certain that the information contained in this book is accurate and that changes have not been made in the recommended dose or in the contraindications for administration. This recommendation is of particular importance in connection with new or infrequently used drugs.

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UNIT 1

GENERAL PRINCIPLES OF TOXICOLOGY

CHAPTER 1

HISTORY AND SCOPE OF TOXICOLOGY

Michael A. Gallo

Toxicology has been defined as the study of the adverse effects of xenobiotics and thus is a borrowing science that has evolved from ancient poisoners. Modern toxicology goes beyond the study of the adverse effects of exogenous agents to the study of molecular biology, using toxicants as tools. Historically, toxicology formed the basis of therapeutics and experimental medicine. Toxicology in this century (1900 to the present) continues to develop and expand by assimilating knowledge and techniques from most branches of biology, chemistry, mathematics, and physics. A recent addition to the field of toxicology (1975 to the present) is the application of the discipline to safety evaluation and risk assessment.

The contributions and activities of toxicologists are diverse and widespread. In the biomedical area, toxicologists are concerned with mechanisms of action and exposure to chemical agents as a cause of acute and chronic illness. Toxicologists contribute to physiology and pharmacology by using toxic agents to understand physiological phenomena. They are involved in the recognition, identification, and quantification of hazards resulting from occupational exposure to chemicals and the public health aspects of chemicals in air, water, other parts of the environment, foods and drugs. Traditionally, toxicologists have been intimately involved in the discovery and development of new drugs and pesticides. Toxicologists also participate in the development of standards and regulations designed to protect human health and the environment from the adverse effects of chemicals. Environmental toxicologists (a relatively new subset of the discipline) have expanded toxicology to study the effects of chemicals in flora and fauna. Molecular toxicologists are studying the mechanisms by which toxicants modulate cell growth and differentiation and cells respond to toxicants at the level of the gene. In all branches of toxicology, scientists explore the mechanisms by which chemicals produce adverse effects in biological systems. Clinical toxicologists develop antidotes and treatment regimes to ameliorate poisonings and xenobiotic injury. Toxicologists carry out some or all of these activities as members of academic, industrial, and governmental organizations. In doing so, they share methodologies for obtaining data about the toxicity of materials and the responsibility for using this information to make reasonable predictions regarding the hazards of the material to people and the environment. These different but complementary activities characterize the discipline of toxicology.

Toxicology, like medicine, is both a science and an art. The science of toxicology is defined as the observational and data-gathering phase, whereas the art of toxicology consists of the utilization of the data to predict outcomes of exposure in human and animal populations. In most cases, these phases are linked because the facts generated by the science of toxicology are used to develop extrapolations and hypotheses to explain the adverse effects of chemical agents in situations where there is little or no information. For example, the observation that the administration of TCDD (2,3,7,8-tetrachlorodibenzo-*p*-dioxin) to female Sprague-Dawley rats induces hepatocellular carcinoma is a fact. However, the conclusion that it will also do so in humans is a prediction or hypothesis. It is important to distinguish facts from predictions. When we fail to distinguish the science from the art, we confuse facts with predictions and argue that they have equal validity, which they clearly do not. In toxicology, as in all sciences, theories have a higher level of certainty than do hypotheses, which in turn are more certain than speculations, opinions, conjectures, and guesses. An insight into modern toxicology and the roles, points of view, and activities of toxicologists can be obtained by examining the historical evolution of the discipline.

HISTORY OF TOXICOLOGY

Antiquity

Toxicology dates back to the earliest humans, who used animal venoms and plant extracts for hunting, warfare, and assassination. The knowledge of these poisons must have predated recorded history. It is safe to assume that prehistoric humans categorized some plants as harmful and others as safe. The same is probably true for the classification of snakes and other animals. The Ebers papyrus (circa 1500 B.C.) contains information pertaining to many recognized poisons, including hemlock (the state poison of the Greeks), aconite (a Chinese arrow poison), opium (used as both a poison and an antidote), and metals such as lead, copper, and antimony. There is also an indication that plants containing substances similar to digitalis and belladonna alkaloids were known. Hippocrates (circa 400 B.C.) added a number of poisons and clinical toxicology principles pertaining to bioavailability in therapy and overdosage, while the Book of Job (circa 400 B.C.) speaks of poison arrows (Job 6:4). In the literature of ancient Greece, there are several references to poisons and their use. Some interpretations of Homer have Odysseus obtaining poisons for his arrows (Homer, circa 600 B.C.). Theophrastus (370–286 B.C.), a student of Aristotle, included numerous references to poisonous plants in *De Historia Plantarum*. Dioscorides, a Greek physician in the court of the Roman emperor Nero, made the first attempt at a classification of poisons, which was accompanied by descriptions and drawings. His classifiction into plant, animal, and mineral poisons not only remained a standard for 16 centuries but is still a convenient classification (Gunther, 1934). Dioscorides also dabbled in therapy, recognizing the use of emetics in poisoning and the use of caustic agents and cupping glasses in snakebite. Poisoning with plant and animal toxins

was quite common. Perhaps the best known recipient of poison used as a state method of execution was Socrates (470–399 B.C.), whose cup of hemlock extract was apparently estimated to be the proper dose. Expeditious suicide on a voluntary basis also made use of toxicological knowledge. Demosthenes (385–322 B.C.), who took poison hidden in his pen, was one of many examples. The mode of suicide calling for one to fall on his sword, although manly and noble, carried little appeal and less significance for the women of the day. Cleopatra's (69–30 B.C.) knowledge of natural primitive toxicology permitted her to use the more genteel method of falling on her asp.

The Romans too made considerable use of poisons in politics. One legend tells of King Mithridates VI of Pontus, whose numerous acute toxicity experiments on unfortunate criminals led to his eventual claim that he had discovered an antidote for every venomous reptile and poisonous substance (Guthrie, 1946). Mithridates was so fearful of poisons that he regularly ingested a mixture of 36 ingredients (Galen reports 54) as protection against assassination. On the occasion of his imminent capture by enemies, his attempts to kill himself with poison failed because of his successful antidote concoction, and he was forced to use a sword held by a servant. From this tale comes the term "mithridatic," referring to an antidotal or protective mixture. The term "theriac" also has become synonymous with "antidote," although the word comes from the poetic treatise *Theriaca* by Nicander of Colophon (204–135 B.C.), which dealt with poisonous animals; his poem "Alexipharmaca" was about antidotes.

Poisonings in Rome reached epidemic proportions during the fourth century B.C. (Livy). It was during this period that a conspiracy of women to remove men from whose death they might profit was uncovered. Similar large-scale poisoning continued until Sulla issued the *Lex Cornelia* (circa 82 B.C.). This appears to be the first law against poisoning, and it later became a regulatory statute directed at careless dispensers of drugs. Nero (A.D. 37–68) used poisons to do away with his stepbrother Brittanicus and employed his slaves as food tasters to differentiate edible mushrooms from their more poisonous kin.

Middle Ages

Come bitter pilot, now at once run on
The dashing rocks thy seasick weary bark!
Here's to my love! O true apothecary!
Thy drugs are quick. Thus with a kiss I die.
Romeo and Juliet, act 5, scene 3

Before the Renaissance, the writings of Maimonides (Moses ben Maimon, A.D. 1135–1204) included a treatise on the treatment of poisonings from insects, snakes, and mad dogs (*Poisons and Their Antidotes*, 1198). Maimonides, like Hippocrates before him, wrote on the subject of bioavailability, noting that milk, butter, and cream could delay intestinal absorption. Maimonides also refuted many of the popular remedies of the day and stated his doubts about others. It is rumored that alchemists of this period (circa A.D. 1200), in search of the universal antidote, learned to distill fermented products and made a 60% ethanol beverage that had many interesting powers.

In the early Renaissance, the Italians, with characteristic pragmatism, brought the art of poisoning to its zenith. The poisoner became an integral part of the political scene. The records of the city councils of Florence, particularly those of the infamous Council of Ten of Venice, contain ample testimony about the political use of poisons. Victims were named, prices set, and contracts recorded; when the deed was accomplished, payment was made.

An infamous figure of the time was a lady named Toffana who peddled specially prepared arsenic-containing cosmetics (*Agua Toffana*). Accompanying the product were appropriate instructions for its use. Toffana was succeeded by an imitator with organizational genius, Hieronyma Spara, who provided a new fillip by directing her activities toward specific marital and monetary objectives. A local club was formed of young, wealthy married women, which soon became a club of eligible young wealthy widows, reminiscent of the matronly conspiracy of Rome centuries earlier. Incidentally, arsenic-containing cosmetics were reported to be responsible for deaths well into the twentieth century (Kallett and Schlink, 1933).

Among the prominent families engaged in poisoning, the Borgias were the most notorious. However, many deaths that were attributed to poisoning are now recognized as having resulted from infectious diseases such as malaria. It appears true, however, that Alexander VI, his son Cesare, and Lucrezia Borgia were quite active. The deft application of poisons to men of stature in the Catholic Church swelled the holdings of the papacy, which was their prime heir.

In this period Catherine de Medici exported her skills from Italy to France, where the prime targets of women were their husbands. However, unlike poisoners of an earlier period, the circle represented by Catherine and epitomized by the notorious Marchioness de Brinvillers depended on developing direct evidence to arrive at the most effective compounds for their purposes. Under the guise of delivering provender to the sick and the poor, Catherine tested toxic concoctions, carefully noting the rapidity of the toxic response (onset of action), the effectiveness of the compound (potency), the degree of response of the parts of the body (specificity, site of action), and the complaints of the victim (clinical signs and symptoms).

The culmination of the practice in France is represented by the commercialization of the service by Catherine Deshayes, who earned the title "La Voisine." Her business was dissolved by her execution. Her trial was one of the most famous of those held by the Chambre Ardente, a special judicial commission established by Louis XIV to try such cases without regard to age, sex, or national origin. La Voisine was convicted of many poisonings, with over 2000 infants among her victims.

Age of Enlightenment

All substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy.
Paracelsus

A significant figure in the history of science and medicine in the late Middle Ages was the renaissance man Philippus Aureolus Theophrastus Bombastus von Hohenheim-Paracelsus (1493–1541). Between the time of Aristotle and the age of Paracelsus, there was little substantial change in the